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Item 4880

PROPOSED 1: 12/2000

United States Environmental Protection Agency
Office of Pollution Prevention and Toxics

CHLOROMETHYL METHYL ETHER, TECHNICAL GRADE
(CAS Reg. No. 107-30-2)

PROPOSED ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

"PUBLIC DRAFT"

Federal Register – December 2000

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Oak Ridge National Laboratory, managed by UT-Battelle, LLC, for the U.S. Dept. of Energy under contract DE-AC05-00OR22725

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. AEGL-2 and AEGL-3 levels, and AEGL-1 levels as appropriate, will be developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and will be distinguished by varying degrees of severity of toxic effects. It is believed that the recommended exposure levels are applicable to the general population including infants and children, and other individuals who may be sensitive and susceptible. The three AEGLs have been defined as follows:

AEGL-1 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing odor, taste, and sensory irritation, or certain non-symptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL level, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL level. Although the AEGL values represent threshold levels for the general public, including sensitive subpopulations, it is recognized that certain individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL level.

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EXECUTIVE SUMMARY

Chloromethyl methyl ether (CMME) is a man-made chemical that is highly flammable and a severe respiratory, eye, nose, and skin irritant. Technical grade CMME contains 1-8% bis-chloromethyl ether (BCME) as a contaminant. Since humans are only exposed to technical grade CMME (a great deal of effort is needed to remove "all" BCME from CMME), and the human and animal inhalation exposure data all involved technical grade CMME, the AEGL values derived in this document will address the toxicity and carcinogenicity of technical grade CMME.

Acute exposure to technical grade CMME can lead to delayed fatal pulmonary edema in humans and animals, whereas chronic occupational exposure is linked with small-cell lung carcinoma. The carcinoma has a distinct histology from that of cigarette smoking-associated lung cancer and has a shorter latency period. BCME is a much more potent carcinogen than CMME, and is widely believed to account for most or all of the carcinogenicity of technical grade CMME. The EPA places technical grade CMME (and BCME) in classification A ("human carcinogen") based on sufficient human carcinogenicity data. Technical grade CMME acute inhalation toxicity has been studied in rats, mice, and hamsters. Numerous epidemiological studies describe occupational exposure to technical grade CMME, although CMME concentrations were almost never measured.

No data were available to determine the concentration-time relationship for CMME toxic effects. The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain protective AEGL-2 and AEGL-3 values for 30-480 minutes, n=3 and n=1 were used to extrapolate to durations shorter and longer, respectively, than the exposure duration in the key study (AEGL-1 values were not derived). The 10-minute values were not extrapolated because the NAC determined that extrapolating from $\geq$ 4 hours to 10 minutes is associated with unacceptably large inherent uncertainty, and the 30-minute values were adopted for 10 minutes to be protective of human health.

AEGL-1 values were not recommended because there were no inhalation studies that had endpoints consistent with the definition of AEGL-1.

AEGL-2 values for technical grade CMME were based on a study in which rats were exposed 30 times (probably for 6 hr/day, 5 days/week) to 1 ppm technical grade CMME vapor (Drew et al., 1975). Two rats died (exposure days 16 and 22) but their cause of death was not stated. Some of the rats were allowed to live for their lifetime; they had minimal mucosal effects and several had lung hyperplasia or squamous metaplasia, but no tumors were reported. The AEGL-2 values were based on a single 6-hour exposure, which is expected to cause a similar or lower incidence of hyperplasia and/or metaplasia than 30 exposures. An uncertainty factor of 10 was used: 3 to account for sensitive humans (response to an irritant gas hydrolyzed *in situ* is not likely to vary greatly among humans) and 3 for interspecies extrapolation (little interspecies variability was seen; the key study was repeat-exposure). A modifying factor of 3 was applied to account for potential differences in BCME content of technical grade CMME. The resulting AEGL values were supported by a lifetime CMME rat and hamster study (Laskin et al., 1975) and a 6-month BCME rat and mouse study (Leong et al, 1975, 1981).

CMME AEGL-2 values were also calculated using a BCME inhalation cancer slope factor with extrapolation to ½ to 8 hours, and based on 10^{-4}, 10^{-5}, and 10^{-6} excess cancer risk levels (BCME was assumed to represent 8% of CMME and to account for all CMME carcinogenicity). CMME AEGL-2 values based on the noncarcinogenicity endpoints were lower than those calculated for 10^{-4} excess cancer risk but were similar to or greater than those calculated for 10^{-5} or 10^{-6} excess cancer risk. AEGL-2 values based on the noncarcinogenic endpoints were considered to be more appropriate because only multiple exposures to CMME were shown to result in tumor formation, and AEGL values are applicable to rare events or single, once-in-a-lifetime exposures of small populations in limited geographic areas.

AEGL-3 values were derived from a rat inhalation LC_{50} study where exposure was for 7 hours (Drew et al., 1975). The threshold for lethality, as represented by the LC_{01} (14.8 ppm) calculated using probit analysis, was the AEGL-3 toxicity endpoint. Animals that died, and to a lesser degree, animals surviving to 14 days, had increased relative lung weights, congestion, edema, hemorrhage, and acute necrotizing bronchitis. An uncertainty factor of 10 was used: 3 for sensitive humans (response to an irritant gas hydrolyzed *in situ* is not likely to vary greatly among humans) and 3 for interspecies extrapolation (little interspecies variability was seen, as expected for an irritant gas hydrolyzed *in situ*). An additional modifying factor of 3 was applied to account for potential differences in BCME content of technical grade CMME. Comparable AEGL-3 values were obtained with CMME in a hamster LC_{50} study and in a BCME single-exposure rat study (Drew et al., 1975).

Summary of Proposed AEGL Values for Chloromethyl Methyl Ether (CMME) [ppm(mg/m^3)]						
Level	**10- minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	Not Recommended (No studies available consistent with AEGL-1 definition)					
AEGL-2 (Disabling)	0.076 (0.25)	0.076 (0.25)	0.061 (0.20)	0.038 (0.13)	0.025 (0.082)	Tracheal or bronchial squamous metaplasia; regenerative lung hyperplasia (Drew et al., 1975).
AEGL-3 (Lethal)	1.2 (3.9)	1.2 (3.9)	0.94 (3.1)	0.59 (2.0)	0.43 (1.4)	Lethality threshold for rats (Drew et al., 1975).

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1. INTRODUCTION

Technical grade chloromethyl methyl ether (CMME) is a highly volatile, colorless, flammable liquid with an irritating odor (CHRIS, 1984-5). CMME vapor is a severe respiratory, eye, nose, and skin irritant, and exposure to high air concentrations causes sore throat, fever, chills, and difficulty breathing (Hake and Rowe, 1963). Acute exposure can lead to delayed fatal pulmonary edema. The technical grade chemical contains 1-8% BCME as a contaminant, which is a more potent human carcinogen and is believed to be responsible for most or all of the carcinogenic activity of technical grade CMME (Travenius, 1982; NIOSH, 1994; HSDB, 1998).

CMME and BCME do not occur naturally, and human exposure is limited to occupational settings. CMME is usually prepared "in-house" by passing HCl through a mixture of formalin and methanol, and is used industrially in the manufacture of ion-exchange resins, bactericides, pesticides, dispersing agents, water repellants, solvents for industrial polymerization reactions, and flame-proofing agents (Van Duuren, 1989; Budavari et al., 1996; Kirwin and Galvin, 1993). CMME is very reactive because of the high electronegativity of the oxygen and its attachment to the same carbon atom as chlorine; nucleophilic displacement of the halogen-bearing carbon atom occurs readily and therefore CMME and BCME are referred to as alkylating agents. CMME and BCME react spontaneously with nucleophilic substrates such as DNA without enzymatic conversion (Burchfield and Storrs, 1977). The chemical and physical properties of CMME are listed in Table 1.

CMME and BCME were recognized by the U.S. industry as potent human respiratory carcinogens in the early 1970s, prompting facilities to develop hermetically isolated systems for their use (Travenius, 1982; Collingwood et al., 1987). In 1973, BCME and CMME were listed by OSHA as part of the first 14 chemicals ever to be restricted by Federal regulations because of their human carcinogenicity, effective February 11, 1974 (39 FR 3756) and their use, storage, and handling must be in a controlled area (38 FR 10929). These regulations apply to all preparations containing $\geq$ 0.1% CMME or BCME (by weight or volume). Subsequent studies examined the carcinogenicity of CMME and BCME on animals, although it has been practically impossible to assess the effect of only CMME since it is contaminated with BCME unless extraordinary measures are taken.

The EPA places CMME (and BCME) in classification A ("human carcinogen") based on sufficient human carcinogenicity data. EPA regulates BCME and CMME under the Clean Water Act, CERCLA, RCRA, SARA, and TSCA. Reportable Quantities (RQs) of 10 lb have been established for both compounds under CERCLA. The ACGIH (1996) has classified CMME as a "suspected human carcinogen" (class A2), has assigned no values for a TWA or STEL, and suggests that "it may be desirable to monitor exposures on the basis of BCME (TLV, 0.001 ppm)."

CMME decomposes so rapidly in aqueous solution that its half-life cannot be accurately measured. The $t_{½}$ for hydrolysis of CMME in aqueous isopropanol was extrapolated to be < 1 second in pure water (Tou and Kallos, 1974). In humid air (ambient temperature; 81% relative humidity), both compounds were more stable, although the $t_{½}$ was dependent on the surface (coating) of the container: the $t_{½}$ for BCME was 7-25 hours, and for CMME was

2.3 minutes-6.5 hours (Tou and Kallos, 1974). It has been reported that of the CMME decomposition products in water (methanol, formaldehyde and HCl), the latter two can recombine to form BCME, and that vapors of HCl and formaldehyde, which are commonly used in industries and laboratories, can combine spontaneously in the air to form BCME (although it has not been shown that CMME can be formed spontaneously in air or water). The hydrolysis of CMME is believed to be irreversible, whereas that of BCME is reversible, although the extent of conversion from CMME to BCME in either water or air has not been well characterized (Travenius, 1982).

In 1993, the U.S. International Trade Commission listed Rohm & Haas Co. as the only company producing CMME in the U.S., although the amount produced or sold was not published to avoid disclosure of individual company operations (USITC, 1993). The amount of CMME produced *in situ* during the production of other chemicals, and the companies involved, was not determined.

TABLE 1. Chemical and Physical Data

Parameter	Value	Reference
Synonyms	Chloromethoxymethane, methyl Chloromethyl ether, Monochloromethyl ether, Chlorodimethyl ether, cmme	Budavari et al. 1996
Molecular formula	CH_3OCH_2Cl	Budavari et al. 1996
Molecular weight	80.51	Budavari et al. 1996
CAS Registry Number	107-30-2	IARC, 1974
Physical state	Liquid	Budavari et al. 1996
Color	Colorless	Budavari et al. 1996
Solubility in water	Decomposes in water ($t_{½}$< 0.5 second) to methanol, formaldehyde and HCl	Nelson, 1976; Travenius, 1982; NIOSH, 1994
Vapor pressure	122 mm Hg @ 68°F (20°C) 260 mm Hg @ 20°C	TRIFacts, 1998 HHMI, 1998
Vapor density (air = 1)	2.8	CHRIS, 1984-5
Density (water = 1)	1.0605 at 20/4°C; 1.074 at 20/4°C	IARC, 1974; Kirwin and Galvin, 1993
Melting point	-103.5°C	Verschueren, 1996
Boiling point	59°C @ 760 mm	Budavari et al. 1996
Odor	Irritating Similar to HCl	IARC, 1974 HHMI, 1998
Odor threshold	1.5 ppm - barely detectable 23 ppm - easily detectable	Wagoner et al., 1972
Conversion factors	1 mg/m^3 = 0.304 ppm 1 ppm = 3.29 mg/m^3	Verschueren, 1996

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No quantitative information was located regarding acute exposure to CMME in humans. The vapors are severely irritating and painful to the eyes and nose. Vapor concentrations that are rapidly fatal are "irrespirable" (term used in reference; no further explanation given) for humans, and illness or death that results from exposure to CMME will occur several days after exposure from lung edema or secondary pneumonia (Hake and Rowe, 1963).

Exposure to the CMME contaminant, BCME, for 1-2 minutes at 100 ppm may produce fatal lung injury, whereas a concentration of 100 ppm would incapacitate a person in a few seconds (Flury and Zernik, 1931, cited in Schrenk et al., 1933).

2.2. Nonlethal Toxicity

No short-term studies were located describing nonlethal effects of CMME exposure in humans. Its odor was reported to be barely detectable at 1.5 ppm and to be easily detectable at 23 ppm (Wagoner et al., 1972). Another source indicated that the highest tolerable concentration of CMME (or BCME) in air is 5 ppm (Travenius, 1982). One U.S. manufacturer in Michigan set an in-house threshold limit value (TLV) of 1 ppm for CMME in the early years of its use, presumably because the CMME odor was not detected and/or was not irritating at < 1 ppm (Weiss, 1992). This Michigan plant did not have an elevated incidence of respiratory cancer in an industry-wide study by Collingwood et al. (1987). However, a one-hour exposure to 1 ppm is presently considered dangerous to human health according to an in-house exposure standard of a large chemical company (Rohm & Haas, 1998).

BCME was reported to be distinctly irritating to the eyes and mucous membranes at 3 ppm (Travenius, 1982). A several-hour exposure to a concentration that did not reach the threshold of perception caused severe eye damage (severe conjunctivitis with keratitis punctata) that was seen several hours after exposure ceased (Travenius, 1982).

Chronic occupational exposure to CMME resulted in coughing, wheezing, blood-stained sputum, breathing difficulty (dyspnea), and weight loss (NIOSH, 1988). Several long-term occupational exposure studies described nonlethal toxic endpoints, however, respiratory cancer as the endpoint was the principal focus of these studies. Leong et al. (1971) indicated that CMME (and BCME) are a health risk at concentrations that do not produce sensory irritation.

2.2.1. Case Reports

All human case reports were associated with respiratory cancers as an endpoint, and are described in section 2.5 (Cancer).

2.2.2. Accidents

No accidental human exposures to known concentrations of CMME were found in the published literature. Accidental industrial exposure to "rather high" concentrations of CMME caused sore throat, fever, and chills, and the subject was not able to work for 8 days, at which time recovery appeared complete (Hake and Rowe, 1963). Another subject who received "very slight exposure" had difficulty breathing for several days (Hake and Rowe, 1963).

2.2.3. Epidemiological Studies

Numerous epidemiological studies were found describing occupational exposure to CMME (contaminated with BCME), most of these only addressed carcinogenicity as an endpoint and are described in section 2.5. (Cancer). Several studies did describe non-cancerous endpoints, however.

Industrial workers exposed for months to years to CMME (containing BCME) had a dose-related increase in chronic bronchitis, although the exposure concentrations were not available (Weiss and Boucot, 1975; Weiss, 1976, 1977). There was no effect on the workers' ventilatory function, as measured by the forced vital capacity (FVC) and the 1-second forced expiratory volume (FEV_1), suggesting the large airways were normal. The small airways did appear to be affected, though, because the end-expiratory flow rate was below predicted values in a dose-related manner. Cigarette smoking acted synergistically with CMME to produce chronic bronchitis and small airway disorders among the workers (however, there was an inverse relationship between smoking and the induction of lung cancer by CMME; see Section 2.5.1.). When chemical exposure diminished, there was a decrease in coughing and an increase in dyspnea (shortness of breath, severity not recorded).

2.3. Developmental/Reproductive Effects

No studies on the developmental or reproductive effects of CMME in humans were located.

2.4. Genotoxicity

The incidence of chromosomal aberrations was greater in the peripheral lymphocytes of workers exposed to CMME or BCME during the manufacture of ion-exchange resins than in control workers (Sram et al., 1983, 1985). The frequency of aberrations was not related to the years of exposure (1-10 years), but was related to the calculated dose of BCME exposure during the last 3 months (Sram et al., 1985).

Zudova and Landa (1977) cytogenetically scored 22 peripheral lymphocytes/person in a group of 12 workers exposed for 2 years to CMME and BCME. Exposed persons had an average of 6.7% aberrant cells compared to 2% in the controls. Blood samples taken from 10 workers after their holidays (length not defined) showed only 3.1% aberrant cells.

CMME was cytotoxic (inhibited scheduled DNA synthesis) in human lymphocytes treated for 4 hours with 10^{-2} M CMME (reported to be "97-99% pure"), although the cytotoxicity was

reversed in the presence of metabolic activation with rat liver phenobarbital-induced S-9 mix (Perocco et al., 1983). CMME (10^{-2} to 10^{-3} M or 5 µL/mL) also increased *in vitro* DNA repair in the presence of metabolic activation, seen as an increased incorporation of tritiated thymidine (Perocco and Prodi, 1981; Perocco et al., 1983).

2.5. Carcinogenicity

2.5.1. Technical Grade CMME Exposure

The U.S. EPA has designated technical grade CMME (and BCME) as group A ("human carcinogen") based on an increased incidence of respiratory cancer in exposed workers (IRIS, 1998). This was supported by evidence of respiratory tumors in mice, rats, and hamsters exposed by inhalation (IRIS, 1998). The ACGIH classified CMME as a Class A2, "suspected human carcinogen," and IARC placed technical grade CMME in Group 1 (sufficient evidence for carcinogenicity to humans and to animals; IARC, 1987). In the available epidemiologic studies, there was a clear trend of an increasing incidence of lung cancer with increasing dose (longer and/or more intense exposure). Several studies showed that the incidence of cancer peaked about 15-20 years post-exposure, thereafter declining (Weiss 1982, Maher and DeFonso, 1987). Exposed humans had elevated rates of respiratory cancer, but not of other types of cancer. The cases occurred at a younger age than lung cancer in the general population, especially among non-smokers. Most frequently the cancer histology was small-cell carcinoma, with a high fraction of these being oat-cell carcinoma, in contrast to lung cancer caused by cigarette smoking, which is predominantly squamous cell carcinoma (Weiss and Boucot, 1975). The air concentrations of CMME in the workroom air were almost never measured, although Travenius (1982) has estimated that they might have been 1-10 ppm, as higher concentrations would have been intolerable.

In 1972, four workers at a California chemical plant of about 100-200 workers (Diamond Shamrock Co., Redwood City) involved in anion-exchange resin production (i.e. exposed to CMME and BCME) died from lung cancer and two more workers developed lung cancer (Anonymous, 1972). The concentration of CMME or BCME in the air was not given. One of the workers that died, a 32-year old male, had been working in the plant only 2 years. Subsequent analysis of exfoliated cells of the sputum of the workers for metaplasia and atypia found no difference between in-plant workers not involved in CMME/BCME production and the controls (Lemen et al., 1976). A significant association was found between abnormal cytology and exposure to CMME/BCME for more than 5 years (34% of anion-exchange workers vs. 11% for controls). In concert with this cytology survey, a retrospective cohort study was initiated in the plant of 136 males having worked 5 years by 3/31/72 (exposure was for a mean of 10 years). Five cases of bronchogenic cancer (3 deaths) were found, as compared to 0.54 cases expected (in white, age-matched males from Connecticut). The mean age of the cancer patients was 47 years, and the predominant histologic type of carcinoma was small cell-undifferentiated. The majority had smoked cigarettes.

A non-smoking German research chemist exposed for 2 years to high concentrations of CMME and BCME died 12 years later (at age 45) of heart circulation failure resultant from pulmonary adenocarcinoma cachexia (Reznik et al., 1977). A 42-year old chemist exposed to

CMME and BCME by inhalation for 7 years died from extensive pulmonary carcinoma (Bettendorf, 1977). The air concentrations of CMME or BCME were not given in either report.

Workers exposed to low concentrations of CMME (containing 4-5% BCME) at least 6 months in a workplace in France from 1959-1971 did not have increased rates of respiratory cancers (Schaffer et al., 1984). The actual concentrations of air CMME were not given. The study author speculated that an increased cancer incidence may not have been found because a limited number of people were included in the study (a total of 670, of which 168 were exposed to CMME), and the observation period may have been too short.

Technical grade CMME (unspecified BCME content) was used in the production of anion exchange resins in a factory (Rohm and Haas) in Chauny, France from 1958 to the end of the study period on December 31, 1986 (Gowers et al., 1993). The air levels of CMME in the factory were not measured but air BCME concentrations were monitored from 1979-1984 with personal and stationary air sampling devices. Approximate annual concentrations of 0.6-4.4 ppb BCME were obtained, with an overall weighted average of 1.7 ppb BCME. Standardized for age, workers with jobs involving exposure to CMME (258 males) had a higher incidence of lung cancer than non-exposed workers (945 males) in the same plant (rate ratio (RR) = 5.0, 95% CI = 2.0-12.3) and greater than an external reference population (RR = 7.6, 95% C.I.= 4.3-13.5). Increased cumulative exposure was associated with an increased incidence of cancer but not with the time from first exposure to diagnosis, which was about 13 years. Exposed workers developed cancer an average of 10.5 years earlier than non-exposed workers. Of the cancers from exposed cases, 10/11 were small-cell, mostly oat-cell, whereas in the non-exposed group only 1/8 cancers were small-cell (16-33% were reported in the external reference population). Smoking history was not known, but reportedly a large fraction of the workers smoked. The observed/expected lung cancer ratio decreased as the exposure concentrations decreased over the years. It is likely that the cancer cases found during the period of BCME monitoring were actually due to previous, much higher exposures before engineering controls were put in place at the plant in 1984.

The finding of 3 cases of lung cancer (men aged 33-39) among about 45 workers who all worked in the production of CMME (0.5-4% BCME) in one building of a large Philadelphia chemical plant in 1962 (Rohm and Haas, about 2500 employees) prompted subsequent studies of the carcinogenic risk of potentially exposed workers in this plant. Air CMME or BCME concentrations were not measured but were retrospectively estimated on a scale of 0-6, where 0 represented “essentially” no exposure.

Figueroa et al (1973) studied a group of 125 men, some of whom were exposed to CMME in this Philadelphia plant. Of the 125 workers, 96 were current cigarette smokers, 13 were nonsmokers, 10 smoked cigar or pipe only, and 6 were former smokers (Weiss and Boucot, 1975). Fourteen of the 125 men were lost to the study due to termination of employment. Fourteen cases of lung cancer developed in men aged 33-55 from 1962 to 1971; these men were exposed 3-14 years with one exception (uncertain duration; possibly one year). Thirteen cancers were oat-cell carcinomas, one was of unknown histologic type. Three of the 13 cancers occurred in non-smokers. The workers were periodically examined (chest photofluorogram and questionnaire) over a 5-year period (1963-1968) during which time 4 cancers developed: these occurred in men aged 35-54 years (88 men were in this age group), which was a roughly an 8 fold

increase in incidence of cancer over the control group. Brown and Selvin (1973) asserted that the actual increase was 44-fold, and that Figueroa et al. (1973) had used an inappropriate control group (too old) and that all 111 men and not just the 88 men between ages 35-54 should have been included.

A ten-year prospective study of this same cohort of 125 men from January 1963 to December 1972 revealed a strong dose-response relationship for bronchogenic cancer (all small-cell carcinomas) among the men exposed for at least 3 months (Weiss and Boucot, 1975, Weiss 1980). The exposed workers had symptoms such as dose-related chronic bronchitis, and the end-expiratory flow rate was below predicted values in a dose-related manner (Weiss, 1977). When chemical exposure diminished, there was a decrease in coughing and an increase in dyspnea (shortness of breath, severity not recorded). Significantly increased risk occurred only among men with moderate or heavy exposure; these workers had an inverse relationship between smoking and the incidence of lung cancer (Weiss and Boucot, 1975; Weiss, 1976, 1977, Weiss et al., 1979). This is in marked contrast to findings with other industrial carcinogens (e.g. asbestos or uranium workers), where cancer was rarely induced without smoking being a cofactor (Travenius, 1982). It is unknown how or whether chronic cigarette smoking was inhibiting development of cancer form CMME/BCME, but Weiss (1980) postulates that the additional or altered viscosity secretions or increased thickness of the mucous covering the bronchial epithelium of the cigarette smokers may be protecting the CMME workers by chemically neutralizing or separating the CMME hydrolysis products from the lung epithelium.

A retrospective study conducted from 1973-June 1974 in the same Philadelphia plant by DeFonso and Kelton (1976) involved all workers (669 men) exposed to CMME from 1948-1972. They had a statistically significant (3.8-fold) increase in lung cancer compared to unexposed workers (1616 men). Dose-response relationships were evident between the incidence of lung cancer and the duration and/or intensity of exposure. There was no correlation between age at first exposure and the time from the first exposure to death, the latter being from 8.3-25.2 years for men beginning their exposure in their late twenties. An additional 9-year follow-up of essentially this same group of men and also summer and short-term employees (737 total exposed; 2120 total unexposed) also showed a dose-related increase in the incidence of respiratory cancer in exposed workers (obs=32, 11.5 =exp; obs/exp=2.79, $p<0.01$; Maher and DeFonso, 1987). At the lowest doses, there was no increase in cancer risk (obs/exp=1.02) whereas at the highest doses the risk was > 10-fold. Most of the cases of respiratory cancer (20/32) had a latency period of 10-20 years. Smoking was not used to adjust the cancer risk because complete information was unavailable, although exposed and non-exposed workers had similar smoking habits. The respiratory cancer incidence decreased in parallel (after an induction period), with the decreased exposure of the workers to CMME/BCME as workplace engineering controls were adopted.

These findings agree with those of Weiss (1982) who studied a cross-section of 125 men employed at this Philadelphia plant in 1963, and followed them from January 1963-December 1979. Weiss (1982) showed that there was a small “epidemic” of respiratory cancer, including 14 cases of lung cancer and 2 cases of laryngeal cancer during this period compared to 2 cases of lung cancer among 34 unexposed men (0.51 expected). This epidemic peaked 15-19 years after the onset of exposure and began to subside thereafter (as workplace exposure decreased). The SMR (standard mortality ratio) for lung cancer was determined to be 8.45 (white Philadelphia

males as reference). Almost all the cases (13/14) of lung cancer were small-cell carcinomas (one was large-cell); the 2 laryngeal cancers were squamous cell carcinomas. The latency period ranged from 10-23 years. All the cancer cases occurred in men with moderate to heavy exposure. CMME was first used at the plant in 1948; 24 years later, the SMR was no longer statistically increased as process improvements over time decreased worker exposure.

The lung mortality patterns of 1794 employees (all males; the < 10 females were excluded) exposed to CMME (2-8% BCME) from 1948-1972 at 6 companies in the U.S. (accounting for the vast majority of U.S. exposure) were examined by Albert et al. (1975) and Pasternack et al. (1977). The control group was the non-exposed men working in the companies during the same time. No CMME/BCME exposure concentrations were available. About 98% of the workers were white; race was not considered in the analysis. The age-adjusted rates for non-cancer death and for overall cancer death were comparable in control and exposed men, whereas the age-adjusted respiratory cancer death rate was 2.5-fold greater in the exposed workers (1.48 in the exposed group and 0.59 in the control group). Of the 22 respiratory cancer cases in the exposed workers 20 were bronchogenic, one was laryngeal, and the other mediastinal. At one of the firms (company 2, probably Rohm & Haas in Philadelphia, PA), where at least 5 years had elapsed since the first exposure, a clear dose-response between exposure and respiratory cancer rate was obtained. All 19 respiratory cancer deaths were seen in workers with heavy exposure, and occurred at an early age of onset (77% occurring before age 55, as compared to 43% in U.S. white males). Smoking histories of the workers were not considered in the analysis.

Collingwood et al. (1987) conducted a 7-year follow-up of workers (1973-1980) at these 6 companies and also the 7th (most recent) major producer of CMME in the US was included for follow-up from 1953 through 1980. At company 7, 26% of the workers were females. Overall, 96% of the workers were male and 97% were white. This study showed that respiratory cancer mortality was increased only at companies 2 (Obs=32, SMR=430) and 7 (obs=9, SMR=603), although the sex of the persons with cancer was not specified. There was a significant exposure-response relationship with respect to cumulative time-weighed exposure. Of the 32 respiratory cancer deaths with verifiable cell type, oat cell carcinoma accounted for the highest proportion (38%), whereas in the non-exposed respiratory cancer deaths the highest proportion (31%) was adenocarcinoma.

Workers were exposed to CMME/BCME in a chemical factory (Rohm & Haas) in Chauny, France, where CMME was used in making anion exchange resins since 1958. Air BCME concentrations were measured from 1979-1984 (Gowers et al., 1993). The yearly average BCME air concentration ranged from 0.6-4.4 ppb BCME, the latter corresponding to 0.044-0.44 ppm CMME if BCME represented 1-10% of the CMME in the air. Although respiratory cancer rates were increased during these years, the workers were not examined after a sufficient latency period and the cancer cases observed were likely due to earlier, substantially higher exposures.

In a group of 318 Shanghai workers (2/3 male, 1/3 female) occupationally exposed to CMME (containing unknown amount of BCME) for at least one year during 1958-1981, there were 16 cancer deaths, of which 12 were lung cancer (Hsueh et al., 1984). The air CMME concentrations were not given and smoking histories of the workers were not reported. Taking into

account the age, sex, and calendar-year specific mortality, the SMR for all cancer was 485, and for lung cancer was 2296, whereas the PMR (proportional mortality ratio) was 219 for all cancer and 855 for lung cancer. All the cancer deaths occurred in male workers; it is unclear whether this was due to different exposures. Illness followed 2-18 years of exposure, the average exposure being 10.5 years. Histological examination of the cancers indicated that 70% were undifferentiated cell type carcinomas (Hsueh et al., 1984).

A study of 276 men working in CMME production (BCME content unknown) at a factory in South Wales between 1948-1980 showed an increased incidence of lung cancer but not other cancer compared to a local unexposed population of 295 men (McCallum et al., 1983). Measurements of air CMME concentrations were not made, but the study author indicated that exposure "may have been high." The rate of cancer deaths was related to total exposure time and average exposure rate, and total dose, but the authors stated that "the degree of exposure appeared to be more important than the duration of exposure in determining carcinogenicity." The incidence of cancer decreased after the manufacturing process was changed to decrease CMME exposure. In another factory in the U.K. (in northeastern England), where air CMME concentrations were "estimated to be low," an increase in cancer rate was not seen (McCallum et al., 1983). The first case of lung cancer was diagnosed about 13 years after production began. Smoking histories of the men were not available.

A chemical plant in Shanghai, China, that produced CMME reported air concentrations of 1.2-59 ppm in 1977-1978, and indicated that the concentrations may have been much higher previously (Wu, 1988). This is inconsistent with the report by Travenius (1982) that the highest tolerable concentration of CMME (or BCME) in air is 5 ppm; the reason for the discrepancy is unknown but may be partly due to analytical differences in air concentration measurements. Of the Chinese workers exposed to CMME for at least one year (534 men and 381 women) from the 1950s through 1981, 15 deaths due to lung cancer were observed compared to 0.97 expected based on Shanghai death rates (SMR=1,546; 95% CI=944-2531). The incidence of death from lung cancer was reportedly related to the amount of CMME exposure but was unrelated to cigarette smoking. Histologic analysis of the lung cancers indicated 8/11 were undifferentiated cell cancers and 3/11 were squamous cell cancers. The average age of death was 50 years (range: 32-64), which was 10 years younger the age of death from cancer in the general Shanghai population. No details of any adverse human toxic response (besides cancer), the method of air concentration analysis, or the level of contaminating BCME were provided.

2.5.2. BCME Exposure

Five of 32 workers exposed to BCME (concentration in air not reported) in a Japanese dyestuff factory for 4-12 years during 1955-1970 died of lung cancer (Sakabe, 1973). This represented a great increase over the expected incidence of lung cancer death rate of 0.024. The men were 37-47 years old at the time of death. One of the five cases was confirmed as being of the oat cell type. Most of the workers were believed to be moderate smokers.

Of 18 production workers exposed to BCME (concentration not given) in a facility in Germany, there were 5 deaths. The workers were exposed for 6 years prior to the diagnoses of cancer (Thiess, 1973).

Three workers died from lung cancer in a small BCME manufacturing facility in the U.K. (Roe, 1985). The exposure concentrations, exposure duration, and the total number of men exposed were not given, but it was stated that "between 5 and 8 individuals were employed at any one time on a process involving a chloromethylation stage." The ages of the men at diagnosis were 35-40 years, and two of the 3 men had oat-cell carcinoma, the third having anaplastic squamous cell carcinoma.

2.6. Summary

No quantitative information was located regarding acute exposure to CMME in humans, although anecdotal reports indicate that the vapors are severely irritating and painful to the eyes and nose. No short-term studies were located describing nonlethal effects of CMME exposure in humans. Chronic exposure to CMME has resulted in coughing, wheezing, blood-stained sputum, breathing difficulty (dyspnea), weight loss, and death from lung cancer.

A number of studies in the U.S. and abroad (Japan, China, the United Kingdom, and France) described occupational exposure to CMME/BCME that was associated with an increased incidence of lung cancer. The lung cancer occurred approximately 10 years earlier than in the general population (who would most likely get it from cigarette smoking), was of a histologic type distinct from that induced by cigarette smoking, and had a dose-response when exposures were estimated semi-quantitatively. In the few rare reports in which actual CMME or BCME air concentrations were given, exposure durations and/or sufficient follow-up were not conducted to allow quantitation of the relationship between exposure and cancer development.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Lethality resulting from acute inhalation exposure to technical grade CMME has been reported for rats, mice, and hamsters. Inhalation of 100 ppm CMME can apparently be tolerated (i.e., death does not occur) by animals for several hours (Hake and Rowe, 1963).

3.1.1. Rats

Groups of 6 rats (strain not specified) exposed to 100-10,000 ppm CMME for ½-4 hours experienced marked irritation to the mucous membranes at all concentrations tested (Hake and Rowe, 1963). A 30-minute exposure to 2000 ppm or a 100 ppm exposure for 4 hours was reportedly "dangerous to life," with death usually being due to chemical pneumonia and occurring several days or weeks after exposure. Details of specific concentrations, exposure times, and accompanying animal responses were not given.

Drew et al. (1975) examined the acute inhalation toxicity of CMME (commercially obtained; BCME content not given) using ~8 weeks old male Sprague-Dawley rats. The CMME vapor was generated by bubbling air through or passing it over liquid CMME prior to its introduction into either 128-liter or 1.3 m^3 exposure chambers; air CMME concentration was measured every half hour. Exposure was to 12.5-225 ppm CMME for 7 hours (see Table 2) the observation period was 14 days; the number of exposed animals was not given but appeared to be >10/concentration.

Lungs were removed from each animal and weighed. Damage was measured as an increase of 3 standard deviations in the lung-to-body weight ratio: the ratio for controls was approximately 0.6 and a value of 0.9 was considered to be elevated. [Previous studies with irritants in the same laboratory showed this ratio could provide an objective criterion for the evaluation of lung damage]. Animals given CMME had concentration-related increases in their relative lung weights. Congestion, edema, hemorrhage, and acute necrotizing bronchitis were evident in lungs of animals that died and to a lesser degree, in animals surviving to 14 days. The LC_{50} was graphically estimated by the authors to be 55 ppm.

TABLE 2. Mortality of Rats Exposed to Chloromethyl Methyl Ether for 7 Hours
(Data from Drew et al., 1975)

Exposure conc. (ppm)	% Mortality after 14 days	% Rats with above normal lung-to-body weight ratio[1]	Estimated[2] LC_{50} (ppm)
225	100[3]	80	55
141	100	80	
70	100	90	
54	43	67	
42	225 (25?)[4]	55	
26	110 (10?)[4]	20	
12.5	0	0	

[1]Greater than the control mean plus 3 SD.
[2]LC_{50} values were estimated graphically by the study authors.
[3]All rats were dead after 4 hours of exposure.
[4]The % mortality given appeared to be a typographical error; suggested values are in parentheses.

Sprague-Dawley rats exposed for 7 hours to 0.94-74 ppm BCME had extensive lung damage, mortality, and the 14-day LC_{50} was about 7 ppm; all animals given $\geq$ 9 ppm BCME died within 14 days, most dying on the first post-exposure day (Drew et al., 1975). Lungs showed congestion, edema, and hemorrhage. The incidence of increased lung-to-body weight ratios (an indicator of lung damage) was greater in treated than control animals at all concentrations, and the increase was concentration-related.

Drew et al. (1975) exposed 25 male Sprague-Dawley rats daily for 30 days to 1.0 or 10.0 ppm technical grade CMME (BCME content not given). The exposure time was not given but was likely 6 hours/day [the report in which the 30-exposure experiment was described also included several other single-exposure studies in which exposure duration was 7 hours/day as well as one multiple-exposure study in which exposure was for 6 hours/day, therefore, 6 hours/day is assumed for the 30-exposure study]. In the 10 ppm group, rats began to die on the third exposure day and 22/25 died by day 30. All animals that died had greatly increased lung-to-body weight ratios (up to 2.2, vs. 0.6 for controls), 10/25 had bronchial epithelial hyperplasia, and one rat had squamous metaplasia. Of the rats exposed to 1.0 ppm CMME, one died on the 16th and one on the 22nd exposure day. The cause of death was not given. Of the survivors, 5 were killed at the end of the last exposure: 4 of these had normal lungs and 1/5 had slight bilateral hemorrhage. Five more rats were killed 2 weeks later, and the other 13 rats were observed for their lifetime. No effects on weight gain occurred in the treated rats. The rats that were held for their lifetimes had minimal

mucosal effects; 2/13 had regenerative hyperplasia, one had squamous metaplasia of the bronchial epithelium, and one had squamous metaplasia of the trachea. No tumors or effects on lung-to-body weight ratios were reported.

3.1.2. Mice

No acute lethality studies where mice were exposed to CMME were located. Strain A/Heston male mice given 2.7 - 10.6 ppm BCME of for 6 hours had a 14-day LC_{50} of 5.3 ppm (95% C/L = 3.7-7.6 ppm) (no further experimental details were provided; Leong et al., 1971).

3.1.3. Hamsters

Drew et al. (1975) examined the acute inhalation toxicity of CMME (commercially obtained; BCME content not given) using male Syrian golden hamsters (~6 weeks old). The CMME vapor was generated by bubbling air through or passing it over liquid CMME prior to its introduction into either 128-liter or 1.3 m^3 exposure chambers; air CMME concentration was measured every half hour. Exposure was to 12.5-225 ppm CMME for 7 hours (see Table 3) and observation was for 14 days; the number of exposed animals was not given but appeared to be >10/concentration. Lungs were removed from each animal and weighed. Damage was measured as an increase of 3 standard deviations in the lung-to-body weight ratio: the ratio for controls was approximately 0.6 and a value of 0.8 was considered to be elevated. [Previous studies with irritants in the same laboratory showed this ratio could provide an objective criterion for the evaluation of lung damage.] Animals given CMME had concentration-related increases in their relative lung weights. Congestion, edema, hemorrhage, and acute necrotizing bronchitis were evident in lungs of animals that died and to a lesser degree, in animals surviving to 14 days. The LC_{50} was graphically estimated by the authors to be 65 ppm.

TABLE 3. Mortality of Hamsters Exposed to Chloromethyl Methyl Ether for 7 Hours
(Data from Drew et al., 1975)

Exposure conc. (ppm)	% Mortality after 14 days	% Hamsters with above normal lung-to-body weight ratio[1]	Estimated[2] LC_{50} (ppm)
225	100[3]	90	65
141	70	80	
70	60	100	
54	33	63	
42	0	60	
26	0	10	
12.5	0	0	

[1]Greater than the control mean plus 3 SD.
[2]LC_{50} values were estimated graphically by the study authors.
[3]Two hamsters died during the exposure period.

Syrian golden hamsters exposed for 7 hours to 0.94-74 ppm BCME had extensive lung damage, mortality, and the 14-day LC_{50} was about 7 ppm; all animals given $\geq$ 9 ppm BCME died within 14 days, most dying on the first post-exposure day (Drew et al., 1975). Lungs showed congestion, edema, and hemorrhage. The incidence of increased lung-to-body weight ratios (an

indicator of lung damage) was greater in treated than control animals at all concentrations, and the increase was concentration-related.

3.2. Nonlethal Toxicity

3.2.1. Rats

Leong et al. (1975, 1981) attempted to determine whether there is a non-tumorigenic or no observable effect level for BCME inhalation in rodents. Groups of 120 male rats (Sprague-Dawley Specific Pathogen-free) were exposed to 0, 1, 10, or 100 ppb BCME vapor 6 hr/day, 5 days/week for 6 months (129 exposures) followed by lifetime observation. Some animals were sacrificed after 6 months for specific analyses. Exposure was in a 3.7 m^3 stainless steel chamber where concentrated vapor was delivered via a dual syringe pump and the chamber BCME concentration was measured at least once daily. Parameters assessed included periodic and/or terminal body weights, gross and microscopic pathology, organ weights, hematology (PCV, MHC, RBC and WBC count, and differential WBC count), pulmonary exfoliative cytological examination on day 1 of the post-exposure period, and cytogenetic evaluation of (chromosomes of) bone marrow on day 5 post-exposure.

No treatment-related non-neoplastic gross or microscopic changes, effects on hematology, organ weights, bone marrow cell chromosome integrity, or pulmonary exfoliated cells were seen in any group of rats (Leong et al. 1975, 1981). Neither respiratory tumors nor increased mortality occurred in either rats or mice at 1 or 10 ppb. Rats exposed to 100 ppb BCME, however, had increased mortality starting at the 7^{th} experimental month and all died or were euthanized by the 19^{th} experimental month. Most of the 100 ppb rats developed esthesioneuro-epitheliomas (96/111; 86.5%) and four of these rats also had pulmonary adenoma. The tumors were frequently found 2-7 months post-exposure, with the first case occurring during the 6th month of exposure. Many of these animals had distended GI tract lumens secondary to the nasal obstruction and subsequent mouth breathing.

3.2.2. Mice

Using an upper respiratory tract screening technique (Alarie, 1966) with strain A/Heston male mice, slight irritation was observed when mice were exposed for 60 seconds to 40 ppm CMME (0.3-2.6% BCME; Leong et al., 1971). No further details of the experiment were given by Leong et al., however, in this technique mice are placed in body plethysmographs and a decrease in their breathing rate during the 60-second exposure or during the ensuing 15-minute observation period is considered to indicate irritation. Using the same screening technique (Alarie, 1966), BCME was non-irritating at concentrations as high as 10.6 ppm to A/Heston male mice exposed for 60 seconds (Leong et al., 1971).

A/Heston male mice exposed for 6 hours to 14.6 - 100 ppm CMME (0.3-2.6% BCME) had no deaths within 14 days of exposure (no further details provided; Leong et al., 1971).

To determine whether there is a non-tumorigenic or no observable effect level for BCME inhalation in mice, Leong et al. (1975, 1981) exposed groups of 144-157 male Ha/ICR mice to 0,

1, 10, or 100 ppb BCME vapor 6 hr/day, 5 days/week for 6 months (129 exposures) followed by lifetime observation. Exposure was in a 3.7 m^3 stainless steel chamber where concentrated vapor was delivered via a dual syringe pump; the chamber BCME concentration was measured at least once daily. The mice did not have any signs of eye or nasal irritation at 1-100 ppb BCME and had weight gain comparable to controls, however, mice in all concentration groups and the controls developed ascending urinary tract infections. Mice exposed to 1 or 10 ppb did not develop respiratory tumors or have increased mortality. Mice exposed to 100 ppb had an increased incidence of pulmonary adenomas (8/27 vs. 9/86 for controls) when mice that died prematurely from urinary tract infections were excluded from analysis. The mice did not develop any nasal tumors. Leong et al. (1981) concluded that "10 and 1 ppb appear to be the no-observable-effect-levels for a 6-month exposure period."

3.2.3. Rabbits

A 1% solution of CMME in propylene glycol caused severe irritation and necrosis in rabbit eyes (Hake and Rowe, 1963).

3.3. Developmental/Reproductive Effects

No studies were located assessing developmental or reproductive effects of CMME exposure on animals.

3.4. Genotoxicity

F344 rats given the maximum tolerated concentration of CMME (concentration not given) had a slight but not statistically definitive increase in micronuclei in bone marrow, but had negative results using the HPRT specific locus assay and lung fibroblasts (Heddle et al., 1991).

CMME (5-10 mg) was weakly mutagenic in *Drosophila melanogaster* larvae (Filippova et al., 1967). Viral transformation of SA7/SHE cells was enhanced by CMME in the absence of metabolic activation (Casto, 1981).

CMME (purity unknown) was mutagenic (about 2-fold increase in revertants) in *Salmonella typhimurium* TA98 when tested at a concentration of 1.0 µL/2000 cm^3 in the absence of metabolic activation (Norpoth et al., 1980). BCME tested at a concentration of 0.5 µL/2000 cm^3 in the absence of metabolic activation was weakly mutagenic in *Salmonella typhimurium* TA1535 (Norpoth et al., 1980). Both CMME and BCME were found to be mutagenic in *E. Coli* and/or *Salmonella* by Mukai and Hawryluk (1973), although experimental details were not provided.

Technical grade CMME did not induce synthesis of DNA, RNA, or protein in the epidermis of mice treated dermally with CMME followed by radiolabeled thymidine, cytidine, or leucine; the skin sections appeared normal (Slaga et al., 1973). In the same experiment, BCME inhibited DNA synthesis for up to 24 hours after treatment and increased RNA synthesis maximally after 12 hours (Slaga et al., 1973).

3.5. Carcinogenicity

3.5.1. Technical Grade CMME Exposure

Fifty strain A/Heston male mice were exposed to 2 ppm CMME vapor (0.3-2.6% BCME) for 6 hours/day, 5 days/week, for 101 exposures over 21 weeks, after which time they were sacrificed (Leong et al., 1971). Exposure was in 100-liter acrylate plastic chambers, and the CMME vapor was generated by metering the liquid CMME into the airstream entering the exposure chamber; the analytical concentration of the CMME inside the chamber was not measured. There was no effect on the mortality, body weight or the demeanor of the mice throughout the study. The lungs of all the treated animals, as well as the 49 control males (exposed to filtered room air for 28 weeks) were examined histologically. The incidence and frequency of lung adenomas was increased slightly in the CMME-exposed mice: the number of animals with tumors was 41% in the controls and 50% in the CMME-treated mice, and the mean number of adenomas per tumor-bearing animal was 2.2 for the controls and 3.1 for the CMME-treated mice. It was not stated whether other parts of the respiratory system were examined for tumors in any mice. Microscopically, the tumor cells from control animals were uniform in size and shape whereas tumor cells from the treated animals were less well defined and frequently formed papillary structures among the surrounding lung tissues. The carcinogenic affect of CMME could not be definitively established from this study because of the small amount of contaminating BCME (Leong et al., 1971).

In a lifetime inhalation study conducted by Laskin et al. (1975), 74 male Sprague-Dawley rats and 90 Syrian golden hamsters were given 1 ppm CMME 6 hrs/day, 5 days/wk. There was no

effect on mortality or body weight gain in either species. Histologic examination of the rats' respiratory mucosa showed a marked increase in the incidence of tracheal squamous metaplasia and bronchial hyperplasia compared to control (74 sham exposed) rats, as well as one lung squamous cell carcinoma (with metastasis to the kidneys) and one esthesioneuroepithelioma of the olfactory epithelium. Additionally, one animal had an undifferentiated pituitary tumor that was probably not related to treatment. The treated hamsters had few mucosal differences from the 80 sham exposed controls, although they had more peripheral bronchoalveolar changes including metaplasia and alveolar cell atypia (nuclear abnormality). One exposed hamster had a lung adenocarcinoma and one had a tracheal squamous papilloma (0 in controls).

3.5.2. BCME Exposure

The long-term effect of single 7-hour exposures of BCME was examined in rats and hamsters (25/concentration) by Drew et al. (1975). Rats were given single exposures to 0.7, 2.1, 6.9, or 9.5 ppm BCME and hamsters to 0.7, 2.1, 5.6, or 9.9 ppm BCME. The animals were allowed to live out their lifetimes. Severe life shortening was observed for all but the lowest concentration: the median lifespan for rats exposed to 2.1, 6.9, and 9.5 ppm was 36, 2, and 2 days, respectively, and for hamsters exposed to 2.1, 5.6, and 9.9 ppm was 68, 16, and 4 days, respectively. At 2.1 ppm and higher, both species had severe weight loss and high lung-to-body weight ratios, as well as lung edema, congestion, hemorrhage, and tracheal and bronchial hyperplasia (often atypical), and squamous metaplasia. Animals exposed to 0.7 ppm BCME had respiratory pathological changes similar to those of controls, although there was a marked increase in the incidence of tracheal epithelial hyperplasia in rats (67% vs. 36% in controls) and in pneumonitis in hamsters (67% vs. 23% in controls). Several hamsters administered 0.7 ppm BCME had bronchial or alveolar metaplasia.

Groups of 50 rats and hamsters were given 1, 3, 10, or 30 six-hour exposures to 1 ppm BCME (Drew et al., 1975). All groups receiving 3, 10, or 30 exposures had increased mortality compared to controls. Treated rats and hamsters had generally concentration-related increases in the incidence of tracheal and bronchial hyperplasia and squamous metaplasia (with and without atypia), with minor increases in incidence evident after 1 exposure. Central nervous system effects and extreme irritability were seen in rats and hamsters given 10 or 30 exposures: subarachnoid hemorrhage was seen microscopically in 24% of the rats and 8% of the hamsters given 30 exposures, and in 17% of the rats given 10 exposures.

Male Sprague-Dawley rats (number not given) were exposed by inhalation to 0.1 ppm BCME for 30 exposures (6 hours/day, 5 days/week) with lifetime follow-up (Dulak and Snyder, 1980). Approximately 35% of the animals died with respiratory tract tumors, which were first observed 350 days after the beginning of exposure (further details were not provided in this abstract).

Leong et al. (1975, 1981) exposed groups of 120 male rats (Sprague-Dawley Specific Pathogen-free) and 144-157 male Ha/ICR mice to 0, 1, 10, or 100 ppb BCME vapor for 6 months (129 exposures) followed by lifetime observation to determine whether there is a non-tumorigenic or no observable effect level for BCME inhalation. Animals were exposed for 6 hr/day, 5 days/week in a 3.7 m^3 stainless steel chamber under dynamic airflow conditions. The BCME vapor was a dilution of a primary concentrated 20 or 200 ppm source prepared by

injecting liquid BCME into a bag containing 100 L dry air; the air from the bag was delivered into the exposure chamber airflow using a dual syringe pump. The chamber BCME concentration was measured at least once daily. Parameters assessed in both sexes included periodic body weights and terminal gross and microscopic pathology. Additionally assessed in rats were the organ weights, hematology (PCV, MHC, RBC and WBC count, and differential WBC count), pulmonary exfoliative cytological examination on day 1 of the post-exposure period, and cytogenetic evaluation of (chromosomes of) bone marrow on day 5 post-exposure. No treatment-related non-neoplastic or neoplastic effects were seen in either the rats or mice exposed to 1 or 10 ppb, however, both species had shortened lifetimes and developed respiratory tumors at 100 ppb. Most rats administered 100 ppb BCME developed esthesioneuroepitheliomas (96/111; 86.5%), frequently at 2-7 months post-exposure, with the first case occurring during the 6th month of exposure. Many of these animals had distended GI tract lumens secondary to the nasal obstruction and subsequent mouth breathing. All groups of mice had ascending urinary tract infections, which "may have been aggravated by exposure to BCME" (Leong et al., 1981). Mice exposed to 100 ppb had an increased incidence of pulmonary adenomas (8/27 vs. 9/86 for controls) when mice that died prematurely from urinary tract infections were excluded from analysis; no nasal tumors were seen.

Male Sprague-Dawley rats and Syrian golden hamsters exposed to 0.1 ppm BCME 6 hours/day, 5 days/week for their lifetimes in a study by Kuschner et al. (1975). Due to high mortality, additional groups of rats were given 10, 20, 40, 60, 80 or 100 exposures 0.1 ppm BCME and allowed to live out their lives (20-50 animals per concentration group; 240 controls). Rats given 80 or more exposures had shortened life spans and deceased weight gain. In rats given 80 exposures and then sacrificed, one nasal esthesioneuroepithelioma and one keratinizing squamous cell carcinoma of the lung "appeared" 383 and 578 days, respectively, after the start of exposure (not specified if animals died at this time). Numerous animals given 10-100 exposures developed nasal and/or lung cancers, consisting primarily of either nasal esthesioneuro-epitheliomas (17/40) or lung squamous cell carcinomas (13/40) (only one rat had both types). The shortest number of exposures that resulted in cancer was 10 - a nasal adenocarcinoma in 1/41 rats, the affected rat dying after 652 days. A clear concentration-response was seen in animals given 10-100 doses, when a survival cutoff of 210 days was used. It is possible that some early nasal tumors may have been missed because the nose was not dissected in animals dying early in the study. [Note that this rat study of 10-100 exposures was used by the EPA to calculate the cancer slope factor and unit risk for BCME carcinogenicity.] Of the Syrian golden hamsters (100) given 0.1 ppm BCME 6 hours/day, 5 days/week for their lifetimes, one hamster receiving 334 exposures developed an undifferentiated lung carcinoma (Kuschner et al., 1975).

A/Heston male mice (50) were exposed to 1 ppm BCME vapor for 6 hours/day, 5 days/week, for 82 times over 27 weeks (no explanation was provided for why the exposures spanned such a long time; the animals must not have been treated 5 days/week for some weeks) (Leong et al., 1971). Exposure was in 100-liter acrylate plastic chambers, and the BCME vapor was generated by metering the liquid BCME into the airstream entering the exposure chamber; the analytical concentration inside the chamber was not measured. The lungs of all the treated animals, as well as the 49 control males (exposed to filtered room air for 28 weeks) were examined histologically. Compared to untreated controls, the BCME-exposed mice had an increased incidence (55% vs. 41% for controls) and multiplicity (5.2 vs. 2.2 for controls) of lung adenomas. These mice had

body weight loss, respiratory distress, and 37 died during the exposure period. Gross necropsy revealed 27/47 animals with lung tumors and 11/47 had pinpoint hemorrhages or patchy consolidation in the lungs (3 animals were cannibalized).

3.6. Summary

There was one major study of the acute toxicity of CMME in rats and hamsters, where the LC_{50} based on a 7-hour exposure and 2-week observation period was about 55 ppm for rats and 65 ppm for hamsters (Drew et al., 1975). Death was not immediate, but delayed, and usually resulted from pneumonia. Rats given 30 exposures to 1.0 or 10.0 ppm CMME (probably for 6 hours/day) had premature mortality and lung hyperplasia or metaplasia (Drew et al. 1975). Mice exposed to 2 ppm CMME 6 hours/day for 101 exposures over 21 weeks had a slight increase in lung tumors (Leong et al, 1971). Rats and hamsters exposed to 1 ppm CMME 6 hrs/day, 5 days/wk for lifetime had increased incidences of respiratory tumors (Laskin et al., 1975; Leong et al 1971).

For BCME, the LC_{50} for rats and hamsters, based on a 7-hour exposure and 2-week observation period, was about 7 ppm for both species (Drew et al., 1975). An examination of the long-term effects of a single 7-hour exposure of 0.7-9.5 ppm BCME in rats and hamsters (Drew et al., 1975) showed that respiratory pathological changes were seen at even the lowest concentration (tracheal epithelial hyperplasia in rats and in pneumonitis in hamsters). Rats and hamsters given 1, 3, 10, or 30 six-hour exposures to 1 ppm BCME had generally concentration-related increases in the incidence of tracheal and bronchial hyperplasia and squamous metaplasia (with and without atypia) (Drew et al., 1975). Rats, mice, and hamsters exposed by inhalation to 0.1 ppm BCME for as few as 10 six-hour exposures and followed for life developed respiratory tumors and/or had shortened lifetimes (Kuschner et al., 1975; Leong et al. 1975, 1981; Dulak and Snyder, 1980). No treatment-related non-neoplastic or neoplastic effects were seen in either rats or mice exposed to 1 or 10 ppb for 6 hours/day for 6 months (Leong et al. 1975, 1981).

Both rats and mice appeared to be able to tolerate (i.e. no apparent irritation or effects on animal demeanor) air concentrations of CMME or BCME greater than those producing carcinogenicity and/or toxicity (i.e. > 1 ppm).

No studies were located assessing developmental or reproductive effects of CMME exposure on animals. Both CMME and BCME were genotoxic in *Salmonella typhimurium* in the absence of metabolic activation; CMME also caused a slight increase in bone marrow micronuclei in F344 rats and mutations in *Drosophila melanogaster* larvae (Filippova et al., 1967; Mukai and Hawryluk, 1973; Norpoth et al., 1980, Sram et al., 1983; Heddle et al., 1991).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information was located in the literature regarding CMME metabolism: CMME is completely hydrolyzed almost immediately upon contact with water ($t_{½} < 1$ sec); the reaction is thought to be irreversible (Van Duuren et al., 1972). It therefore seems “unlikely CMME would survive transport in body fluids to organs outside the respiratory system after inhalation” (Weiss,

1992). BCME is slightly less reactive in water ($t_{½}$ for hydrolysis = 30-60 sec.), although it is believed to exist in equilibrium with its hydrolysis products in water, with about 20% of the original compound left (Van Duuren et al., 1972).

4.2. Mechanism of Toxicity

Little is known regarding the mechanism of CMME toxicity. CMME is very reactive because of the high electronegativity of the oxygen and its attachment to the same carbon atom as chlorine (Burchfield and Storrs, 1977). Nucleophilic displacement of the halogen-bearing carbon atom should occur readily and therefore CMME (and BCME) are referred to as alkylating agents. CMME can react spontaneously with nucleophilic substrates such as DNA without enzymatic conversion (Burchfield and Storrs, 1977). Consistent with its in situ hydrolysis and its activity as an alkylating agent, the respiratory tract is the primary site of technical grade CMME toxicity and carcinogenicity in humans and in animals.

CMME hydrolyzes completely and irreversibly in water to form HCl, methanol, and formaldehyde. The HCl and formaldehyde can form BCME, although the kinetics of the conversion of CMME to BCME have not been defined (Travenius, 1982). It is believed that in water BCME is in equilibrium with its hydrolysis products, with about 20% of the original compound left (Van Duuren et al., 1972; Van Duuren 1980).

It has not been determined to what extent technical grade CMME, its hydrolysis products, or any potentially formed BCME are responsible for the toxicity and carcinogenicity of CMME. Comparison of LC_{50} values for CMME and BCME in rats and hamsters (55-65 ppm for CMME; 7 ppm for BCME) indicates that BCME is more acutely toxic by inhalation than CMME (Drew et al., 1975). Animal carcinogenesis studies indicate that BCME is at least 10-fold more potent as a carcinogen than CMME, both by inhalation (Drew et al., 1975; Kuschner et al, 1975; Laskin et al., 1975), and by dermal application and subcutaneous injection (Van Duuren et al., 1968, 1969; Gargus et al., 1969).

Several investigators have suggested that CMME and/or BCME are direct-acting carcinogens that are radiomimetic in the form of injury they induce (Drew et al., 1975; Travenius, 1982). BCME has been shown to react with the guanine and adenine of DNA (Goldschmidt et al., 1975). However, in other *in vitro* studies, neither CMME nor BCME formed any isolable discrete base-alkylation products (by TLC; Van Duuren et al., 1969, 1972) or had any effect on the λ max, T_m, and buoyant density of salmon sperm DNA (Van Duuren et al., 1972).

Drew et al. (1975) examined the extent of degradation of 10 ppm CMME (to form formaldehyde, hydrochloric acid, and methanol) in air in a 128-liter animal exposure chamber. Using the method of Goldman and Yagoda (1943) for the determination of formaldehyde, the investigators found that about 50% of the CMME was degraded. Consistent with this, rats exposed to CMME typically had yellow discoloration of their fur, which was also observed when the rats are exposed to formaldehyde. However, it appears that formaldehyde is not responsible for CMME toxicity because it was much less toxic than CMME alone or with its breakdown in animals studies, and is a much weaker animal carcinogen than technical grade CMME (Drew et al., 1975; Travenius, 1982, IRIS, 1998).

4.3. Structure-Activity Relationships

The chemical most related to technical grade CMME in its behavior is BCME. Its toxicity and carcinogenicity are discussed in the human and animal toxicity and carcinogenicity sections above. In all cases, BCME is more toxic (roughly 10-fold) and more carcinogenic (> 10-fold) than technical grade CMME. One possible exception is odor, with technical grade CMME odor being more readily detected than BCME odor (Rohm and Haas, 1998).

The higher carcinogenicity of BCME compared to CMME is not due to the potential of cross-linking DNA strands of BCME because for cross-linking, the reactive groups of a bifunctional alkylating agent should be able to reach across approximately 8 Å, and the distance between the reactive halogens in BCME is too small for cross-linking to be possible (Burchfield and Storrs, 1977)

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When the chlorine and oxygen atoms are separated in structurally related chloroethers by 2 or more carbon atoms, (e.g. bis(β-chloroethyl) ether), the alkylating power and carcinogenicity are greatly reduced (Burchfield and Storrs, 1977), whereas eye irritation seems to be unaffected by chain length (Kirwin and Galvin, 1993).

4.4. Other Relevant Information

It has been suggested that theoretically, there might be a safe concentration threshold at which all CMME/BCME would be decomposed on the moist mucous membranes of the lung air passages (Travenius, 1982). The work of Leong et al. (1981) in which rats and mice had no detectable physiological responses when exposed to 1 or 10 ppb BCME for 6 months (whereas exposure to 100 ppb caused extensive toxicity and carcinogenicity) suggests that a threshold does exist for BCME (and therefore likely CMME) carcinogenicity.

4.4.1. Species Variability

The study by Drew et al. (1975) indicated that there is not a great deal of variability between species for CMME acute toxicity: the 7-hour LC_{50} for rats and hamsters was 55 and 65 ppm, respectively. This finding is consistent with the fact that CMME is a local-acting chemical (hydrolyzes *in situ*) and therefore metabolism is unlikely play a role in its toxicity.

4.4.2. Concentration-Exposure Duration Relationship

No data were available from which to determine the concentration-time relationship for CMME toxic effects. Ten Berge et al. (1986) determined that the concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. To obtain protective AEGL-2 and AEGL-3 values for 30-480 minutes, n=3 and n=1 were used to extrapolate to durations shorter and longer, respectively, than the exposure duration in the key study using the ten Berge equation (AEGL-1 values were not derived). The 10-minute values were not extrapolated because the NAC determined that extrapolating from ≥ 4 hours to 10 minutes is associated with unacceptably large

inherent uncertainty, in which case the 30-minute value is adopted for 10 minutes to be protective of human health.

4.4.3. Other Routes of Exposure

Technical grade CMME was only moderately toxic given orally to animals. Rabbit skin tests using undiluted CMME resulted in severe hyperemia, edema, denaturation, and even complete destruction of the skin (Hake and Rowe, 1963; NIOSH, 1977).

4.4.4. Neoplastic Potential of CMME by Other Exposure Routes

Purified CMME (99.5%) was not a complete carcinogen or a promoter when 0.1 or 1 mg (as a 2% solution in benzene) was applied topically to the skin of female ICR/Ha Swiss mice trice/week for 325 days in a two-stage mouse skin carcinogenesis study (Van Duuren et al., 1968, 1969). CMME did, however, act as a tumor initiator (papillomas and/or squamous carcinomas) when a single application was given 2 weeks before the promoter (croton resin, given 3x weekly up to 540 days).

Purified CMME (99.5%) injected subcutaneously in female Sprague-Dawley rats (3 mg 1x/week for 114 days, which was reduced due to ulceration to 1 mg 3x/month until day 301) resulted in 14/20 animals having encapsulated nodules at the injection site and 1/20 females had a fibrosarcoma (0/20 in controls; Van Duuren et al., 1968, 1969). In the same study, subcutaneous injection in rats once/week of 3.0 mg BCME in paraffin oil (reduced to 1 mg 3 x/month after 100 days to day 301) resulted in substantial weight loss of the animals and ulceration at the test site; 5/20 animals developed fibrosarcomas (Van Duuren et al., 1968, 1969).

Female ICR/Ha Swiss mice given weekly lifetime subcutaneous injections of 300 µg CMME (99.5% pure) in 0.1 mL nujol (purified paraffin oil) developed local sarcomas at the injection site (10/30 compared to 0/30 controls; Van Duuren at al., 1972).

A single subcutaneous injection of 125 µL/kg (0.17 mg/kg) CMME (0.3-2.6% BCME) in peanut oil was given to newborn ICR Swiss mice (1-3 days old; 48 F, 51 M) that were killed after 6 months. Treated mice had a slightly increased incidence and multiplicity of pulmonary adenomas: incidence of 17% for treated and 14% for controls; multiplicity of 0.21 for treated and 0.14 for controls (Gargus et al., 1969). Growth and survival of the mice were comparable to those of the vehicle control mice. Gargus et al. (1969) indicated that it was possible that this small increase in the incidence of adenomas was due to the contaminating BCME. In the same study, newborn mice injected with 0.016 mg/kg BCME in peanut oil had a 45% incidence and 0.64 multiplicity of pulmonary adenomas. A positive control group of 50 mice injected once with 1500 mg/kg urethane had a 100% incidence of lung tumors with a multiplicity of 17 (Gargus et al., 1969).

5. RATIONALE AND PROPOSED AEGL-1

5.1. Human Data Relevant to AEGL-1

No short-term studies were located describing nonlethal effects of technical grade CMME exposure in humans. Its odor threshold is reportedly ~1.5 ppm (Wagoner et al., 1972). One U.S. manufacturer in Michigan set an in-house threshold limit value (TLV) of 1 ppm for technical grade CMME in the early years of its use (Weiss, 1992); this plant did not have an elevated incidence of respiratory cancer (Collingwood et al., 1987). However, exposure to 1 ppm technical grade CMME for one hour is currently considered dangerous to human health according to the an in-house exposure standard of a large chemical company (Rohm & Haas, 1998).

Numerous epidemiological (chronic exposure) studies were found describing occupational exposure to technical grade CMME, although CMME air concentration was reported in only one occupational exposure study (1.2-59 ppm for ≥1 year; Wu, 1988). This study is not consistent with a report by Travenius (1982) that the highest tolerable concentration of CMME (or BCME) in air is 5 ppm; the reason for the discrepancy is unknown. In any case, the Wu study is not appropriate for AEGL-1 derivation because the exposure length is too long.

The CMME contaminant BCME was reported to be distinctly irritating at 3 ppm (Flury and Zernik, 1931, cited in Schrenk et al., 1933).

5.2. Animal Data Relevant to AEGL-1

Using an upper respiratory tract screening technique (Alarie, 1966) in which A/Heston male mice received a 60-second exposure to CMME (containing 0.3-2.6% BCME) and were observed for the next 15 minutes for a decrease in their breathing rate, slight irritation occurred with exposure to 40 ppm (Leong et al., 1971). Using the same screening technique, BCME was non-irritating at concentrations as high as 10.6 ppm (Leong et al., 1971).

5.3. Derivation of AEGL-1

AEGL-1 values are not recommended, as shown in Table 4, because there were no inhalation exposure studies with technical grade CMME that produced endpoints consistent with the definition of AEGL-1 (see the Preface for the definition).

TABLE 4. AEGL-1 for Chloromethyl Methyl Ether

10-minute	30-minute	1-hour	4-hour	8-hour
Not Recommended (No studies available consistent with AEGL-1 definition)				

6. RATIONALE AND PROPOSED AEGL-2

It is relevant to consider results from both experiments using technical grade CMME and BCME to derive AEGL-2 values. This is because technical grade CMME contains 1-8% BCME, and evidence indicates that a substantial portion of CMME toxicity and/or carcinogenicity may be due to the contaminating BCME. Animal data also supports the possibility that carcinogenesis could result from a single exposure to technical grade CMME: one exposure to ≥ 0.7 ppm BCME

resulted in lung cell alterations that may be pre-neoplastic (Drew et al., 1975), and a rat given only 10 exposures of 0.1 ppm BCME (over 2 weeks) developed a respiratory tumor (Kuschner et al., 1975).

6.1. Human Data Relevant to AEGL-2

No human data were located that were considered appropriate for derivation of AEGL-2 values.

6.2. Animal Data Relevant to AEGL-2

A/Heston male mice exposed for 6 hours to 14.6 - 100 ppm CMME (0.3-2.6% BCME) had no deaths within 14 days of exposure (no further details provided; Leong et al., 1971). The presence of any toxic effects in the animals was not investigated, although the possibility cannot be excluded.

Drew et al. (1975) exposed male rats to 1 ppm technical grade CMME vapor 6 hrs/day (not specified; see Section 3.1.1.), 5 days/week for 30 exposures. Two rats died during exposure (on days 16, 22; cause of death was not reported), 10 were sacrificed immediately or 2 weeks after exposure, and 13 were retained for their lifetime. The lungs of 4/5 rats sacrificed early were normal (one had slight hemorrhage). Several of the rats retained for lifetime study had lung hyperplasia or squamous metaplasia but no tumors were reported.

Male rats and hamsters given lifetime exposures to 1 ppm technical grade CMME 6 hrs/day, 5 days/wk had no effects on mortality or body weight gain (Laskin et al.,1975). Rats had a marked increase in the incidence of tracheal squamous metaplasia and bronchial hyperplasia and two had respiratory tumors. The treated hamsters had an increased incidence of bronchoalveolar metaplasia and alveolar cell atypia (nuclear abnormality). One exposed hamster had a lung adenocarcinoma and one had a tracheal squamous papilloma (0 in controls).

Leong et al. (1975, 1981) conducted a study where male rats and mice were exposed to 0, 1, 10, or 100 ppb BCME vapor 6 hr/day, 5 days/week for 6 months and most animals were retained for lifetime observation (Leong et al. 1975, 1981). No treatment-related toxicity or gross or microscopic changes were found in the rats exposed to 1 or 10 ppb, but animals exposed to 100 ppb had early mortality and developed respiratory tumors (rats: esthesioneuroepitheliomas; mice: pulmonary adenomas).

6.3. Derivation of AEGL-2

The 30-exposure study in which 25 male rats were exposed to 1 ppm technical grade CMME vapor 6 hrs/day (duration not specified but assumed to be 6 hours/day; see Section 3.1.1.), 5 days/week, and most rats were allowed to live for their lifetime (Drew et al., 1975) was considered the best study for derivation of AEGL-2 values. The lungs of 4/5 of the animals sacrificed 0-2 weeks after exposure were normal (one had hemorrhage); a few of the rats retained for lifetime study had lung hyperplasia or squamous metaplasia but no tumors were reported. The

cause of death of the two rats that died during the exposure period (on days 16 and 22) was not specified.

No reliable data were available from which to determine the CMME concentration-time relationship in order to derive AEGL-2 values for time periods other than 6 hours. Ten Berge et al. (1986) showed that the concentration-time relationship for many irritant and systemically acting vapors and gases can be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. To obtain protective AEGL-2 values, scaling across time was performed using n=3 and n=1 for exposure durations shorter and longer, respectively, than 6 hours, except the 10-minute values were not extrapolated because the NAC determined that extrapolating from ≥ 4 hours to 10 minutes is associated with unacceptably large inherent uncertainty, and the 30-minute values were adopted for 10 minutes to be protective of human health. An uncertainty factor of 10 was used: 3 to account for sensitive humans (response to an irritant gas hydrolyzed *in situ* is not likely to vary greatly among humans) and 3 for interspecies extrapolation (the key study was repeat-exposure; CMME is a local-acting irritant (hydrolyzes *in situ*) and metabolism is unlikely play a role in its toxicity). A modifying factor of 3 was additionally applied to account for potential differences in BCME content of technical grade CMME which was used in the animal experiments (reported to vary between 1-8%) and the technical grade CMME to which humans might be exposed. The resulting AEGL-2 values are shown in Table 5; calculations are detailed in Appendix A. The detection level of CMME (and BCME) in the air is < 1 ppb by gas chromatography-mass spectrometry (Travenius, 1982), therefore the AEGL-2 levels are well above the detection limit.

TABLE 5. AEGL-2 for Chloromethyl Methyl Ether [ppm(mg/m^3)]

10-minute	30-minute	1-hour	4-hour	8-hour
0.076 (0.25)	0.076 (0.25)	0.061 (0.20)	0.038 (0.13)	0.025 (0.082)

Although the key AEGL-2 study (Drew et al., 1975) has the drawback that it involves multiple exposures, it has the benefit of lifetime observation of the animals, which is pertinent for a suspected cancer-causing agent. The AEGL-2 values were based on a single 6-hour exposure, reasoning that one 6-hour exposure would cause a similar or lower incidence of hyperplasia and/or metaplasia than 30 exposures. Use of a multiple-exposure study is less than ideal, but tends to err on the conservative (i.e., protective) side, and mitigates some of the uncertainty associated with the two animal deaths on exposure days 16 and 22.

Supportive of the selected key study (yielding the same or similar AEGL-2 values) are two other animal studies: the lifetime 1 ppm CMME rat and hamster exposure study by Laskin et al. (1975) and a 6-month BCME rat and mouse study (6 hours/day at 0.01 ppm; Leong et al, 1975, 1981) when 6 hours is used as the exposure time. In the latter study, CMME concentration was estimated from BCME concentration; AEGL-2 values nearly identical to the key study are obtained when 2.9% BCME is assumed (this value is within the range reported for commercial CMME).

CMME AEGL-2 values were also calculated using a BCME inhalation cancer slope factor and based on 10^{-4}, 10^{-5}, and 10^{-6} excess cancer risk levels, as shown in Appendix B (BCME was assumed to represent 8% of CMME and to account for all of CMME carcinogenicity).

7. RATIONALE AND PROPOSED AEGL-3

It is relevant to consider results from both experiments using technical grade CMME and BCME to derive AEGL-3 values. This is because technical grade CMME contains 1-8% BCME, and evidence indicates that a substantial portion of CMME toxicity and/or carcinogenicity may be due to the contaminating BCME.

7.1. Human Data Relevant to AEGL-3

No quantitative information was located regarding acute exposure to technical grade CMME or BCME in humans. A 1-2 minute exposure to 100 ppm BCME "may produce fatal lung injury" (Flury and Zernik, 1931, cited in Schrenk et al., 1933).

Vapor concentrations of CMME that are rapidly fatal are reportedly "irrespirable" for humans, and illness or death that results from exposure to CMME will occur several days later from lung edema or secondary pneumonia (Hake and Rowe, 1963).

7.2. Animal Data Relevant to AEGL-3

Rats given a 30-minute exposure to 2000 ppm CMME (purity unknown) or a 4-hour exposure to 100 ppm died from chemical pneumonia several days or weeks after exposure (Hake and Rowe, 1963). Further study details were not given.

The LC_{50} values for male rats and hamsters exposed for 7 hours to 12.5-225 ppm technical grade CMME were about 55 ppm for rats and 65 ppm for hamsters; the LC_{50} for rats and hamsters given 0.94-74 ppm BCME for 7 hours was about 7 ppm for both species (Drew et al., 1975). All groups of treated animals that died and to a lesser degree, that survived to 14 days, had concentration-related increases in their relative lung weights, congestion, edema, hemorrhage, and acute necrotizing bronchitis.

Male Sprague-Dawley rats given 30 consecutive daily exposures to 10.0 ppm technical grade CMME (duration not specified but probably 6 hours/day (see Section 3.1.1.) (Drew et al., 1975) began to die on the third exposure day and 22/25 died by day 30. All animals that died had greatly increased lung-to-body weight ratios, 10/25 had bronchial epithelial hyperplasia, and one rat had squamous metaplasia.

Fifty male mice exposed to 2 ppm technical grade CMME vapor (0.3-2.6% BCME) for 6 hours/day, 5 days/week, for 101 exposures over 21 weeks (and then sacrificed) had no effect on their mortality rates, body weight, or demeanor, but had a slightly increased incidence (50% vs. 41% in controls) and multiplicity (3.1 vs. 2.2 for the controls) of lung adenomas (Leong et al., 1971). The morphology of tumor cells from control and treated animals differed.

Male rats and hamsters given lifetime exposure to 1 ppm technical grade CMME (6 hrs/day, 5 days/wk) had no differences from controls in their mortality or body weight gain, but had an increased incidence of pulmonary squamous metaplasia and hyperplasia (Laskin et al., 1975). Two rats (of 74) and two hamsters (of 90) developed respiratory tumors (0 in controls).

Male rats and mice exposed to 100 ppb BCME vapor 6 hr/day, 5 days/week for 6 months (lifetime observation) had early mortality and developed esthesioneuroepitheliomas (86.5% of rats) or pulmonary adenomas (about 30% of mice, 4% of rats), although their body weights were unaffected (Leong et al. 1975, 1981). No treatment-related effects occurred in rats or mice exposed to 1 or 10 ppb BCME for 6 months.

Rats and hamsters given single 7-hour exposures to 0.7-9.9 ppm BCME and retained for their lifetimes had severe life shortening, weight loss, increased lung-to-body weight ratios, lung edema, congestion, hemorrhage, and tracheobronchial hyperplasia and squamous metaplasia at 2.1 ppm and higher (Drew et al., 1975). Rats exposed to 0.7 ppm BCME had an increased incidence of tracheal epithelial hyperplasia whereas hamsters had an increased incidence of pneumonitis and bronchial or alveolar metaplasia.

Rats and hamsters given 3, 10, or 30 six-hour exposures to 1 ppm BCME had increased early mortality and tracheobronchial hyperplasia and squamous metaplasia (Drew et al., 1975). Minor increases in incidence of tracheobronchial hyperplasia and squamous metaplasia were evident after 1 exposure. Central nervous system effects occurred in rats given 10 or 30 exposures.

Male rats given 10, 20, 40, 60, 80, 100, or lifetime exposures to 0.1 ppm BCME (6 hours/day, 5 days/week) and followed for their lifetimes had dose-related increases in nasal or lung cancers, with 1/41 rats receiving 10 doses developing a nasal adenocarcinoma (Kuschner et al., 1975). Rats given 80 or more exposures had shortened life spans and deceased weight gain. [This study was used by the EPA to calculate the unit risk for BCME carcinogenicity.] One of 100 male hamsters given 0.1 ppm BCME 6 hours/day, 5 days/week for their lifetimes developed an undifferentiated lung carcinoma (Kuschner et al., 1975).

7.3. Derivation of AEGL-3

The study considered most appropriate for derivation of AEGL-3 values was the rat and hamster LC_{50} study where each species was exposed to 12.5-225 ppm technical grade CMME for 7 hours and observed for 14 days (Drew et al., 1975). The treated animals that died, and to a lesser degree, those surviving to 14 days had concentration-related increases in relative lung weights, congestion, edema, hemorrhage, and acute necrotizing bronchitis. The rat LC_{01} (14.8 ppm) was used for the AEGL derivation because the majority of the CMME animal studies used rats, and comparison among studies was considered more direct with rat data (the hamster LC_{01} of 10.8 ppm yielded very similar AEGL-3 values). To obtain AEGL-3 values for 30-480 minutes, scaling across time was performed using n=3 and n=1 to for durations shorter and longer, respectively, than 7 hours because no data were available from which to determine the CMME concentration-time relationship (see Section 4.4.2.). The 10-minute values were not extrapolated because the NAC determined that extrapolating from $\geq$ 4 hours to 10 minutes is

associated with unacceptably large inherent uncertainty, and the 30-minute values were adopted for 10 minutes to be protective of human health.

An uncertainty factor of 10 was applied: 3 for interspecies (rat and hamster yielded similar LC_{50} values in the key study) and 3 for intraspecies (CMME is a local-acting irritant (hydrolyzed *in situ*) and metabolism is unlikely to play a role in its toxicity). An additional modifying factor of 3 was applied to account for potential differences in BCME content of technical grade CMME which was used in the animal experiments (reported to vary between 1-8%). The resulting AEGL-3 values are shown in Table 6; calculations are detailed in Appendix A. AEGL-3 values similar to these were obtained using hamster CMME LC_{01} data and a BCME single-exposure rat study (Drew et al., 1975).

TABLE 6. AEGL-3 for Chloromethyl Methyl Ether [ppm(mg/m^3)]

10-minute	30-minute	1-hour	4-hour	8-hour
1.2 (3.9)	1.2 (3.9)	0.94 (3.1)	0.59 (2.0)	0.43 (1.4)

8. SUMMARY OF PROPOSED AEGLs

8.1. AEGL Values and Toxicity Endpoints

A summary of the proposed AEGL values for technical grade CMME and their relationship to one another are shown in Table 7. No data were available to determine the concentration-time relationship for CMME toxic effects. Scaling across time for 30-480 minutes was performed using the relationship $C^n \times t = k$, with n=3 and n=1 being used to extrapolate to durations shorter and longer, respectively, than the exposure duration in the key study. The 10-minute values were not extrapolated because the NAC determined that extrapolating from $\geq$ 4 hours to 10 minutes is associated with unacceptably large inherent uncertainty, and the 30-minute values were adopted for 10 minutes to be protective of human health.

AEGL-1 values were not derived because there were no inhalation exposure studies with technical grade CMME that produced endpoints consistent with the definition of AEGL-1.

The AEGL-2 was based on a study in which 25 male rats were exposed to 1 ppm technical grade CMME vapor 6 hr/day (not specified but 6 hrs/day was assumed; see Section 3.1.1.), 5 days/week for 30 exposures (Drew et al., 1975). Two rats died during exposure (on days 16, 22; cause of death not reported). The lungs of 4/5 rats sacrificed after 30 exposures were normal (one had slight hemorrhage). Of the 13 rats retained for lifetime study, most had minimal mucosal effects, two had regenerative hyperplasia, one had bronchial and one had tracheal squamous metaplasia but no tumors were reported. An uncertainty factor of 10 was used: 3 to account for sensitive humans (response to an irritant gas hydrolyzed *in situ* is not likely to vary greatly among humans) and 3 for interspecies extrapolation (little interspecies variability was seen; the key study was repeat-exposure). A modifying factor of 3 was additionally applied to account for potential differences in BCME content of technical grade CMME. Similar AEGL-2 values were obtained from a lifetime CMME exposure study (Laskin et al., 1975) and from a 6-month BCME exposure

study (Leong et al, 1975, 1981). In the latter study, CMME concentration was estimated from BCME concentration by assuming BCME represents 1-8% of technical grade CMME.

CMME AEGL-2 values were also calculated using a BCME inhalation cancer slope factor with extrapolation to ½ to 8 hours, and based on 10^{-4}, 10^{-5}, and 10^{-6} excess cancer risk levels (BCME was assumed to represent 8% of CMME and to account for all of CMME carcinogenicity). CMME AEGL-2 values based on the noncarcinogenicity endpoint were lower than those calculated for 10^{-4} excess cancer risk but were similar to or greater than those calculated for 10^{-5} or 10^{-6} excess cancer risk. AEGL-2 values based on noncarcinogenic endpoints were considered to be more appropriate because only multiple exposures to CMME were shown to result in tumor formation and AEGL values are applicable to rare events or single, once-in-a-lifetime exposures of small populations in limited geographic areas.

The AEGL-3 was based on the LC_{01} (14.8 ppm) calculated by probit analysis from a rat 7-hour exposure LC_{50} study (Drew et al., 1975). Animals that died, and to a lesser degree, animals surviving to 14 days, had increased relative lung weights, congestion, edema, hemorrhage, and acute necrotizing bronchitis. An uncertainty factor of 10 was used: 3 for sensitive humans (response to an irritant gas hydrolyzed *in situ* is not likely to vary greatly among humans) and 3 for interspecies extrapolation (little interspecies variability was seen, as expected for an irritant gas hydrolyzed *in situ*). An additional modifying factor of 3 was applied to account for potential differences in BCME content of technical grade CMME. AEGL-3 values similar to these were obtained using hamster LC_{01} CMME data and a rat BCME single-exposure study (Drew et al., 1975).

TABLE 7. Summary of AEGL Values for Chloromethyl Methyl Ether [ppm(mg/m^3)]

Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	(No studies available consistent with AEGL-1 definition)				
AEGL-2	0.076 (0.25)	0.076 (0.25)	0.061 (0.20)	0.038 (0.13)	0.025 (0.082)
AEGL-3	1.2 (3.9)	1.2 (3.9)	0.94 (3.1)	0.59 (2.0)	0.43 (1.4)

8.2. Comparison with Other Standards and Criteria

There are no U.S. standards for exposure to technical grade CMME due to its known human carcinogenicity. A Threshold Limit Value of 0.001 ppm was listed under "Health Hazards" by the Chemical Hazard Response Information System (CHRIS, 1984-5).

A large chemical manufacturer in Philadelphia has developed internal ERPG values (1-hour exposure) for technical grade CMME of 10 ppb for the ERPG-2 and 1 ppm for ERPG-3 (no ERPG-1); the respective ERPG values for BCME are 10-fold lower (Rohm and Haas, 1998).

8.3. Data Quality and Research Needs

No studies were found with defined exposures and responses that fell within the scope of AEGL-1. This is due to the fact that CMME was toxic to animals and humans at concentrations below the odor detection level (e.g. the proposed AEGL-3 values are in the barely detectable range for humans).

Appropriate single-exposure studies with AEGL-2 endpoints were also lacking; the available information was incomplete with respect to the exposure concentration and/or duration. Although use of multiple-exposure studies as the basis for AEGL-2 values is less than ideal, it tends to err on the conservative (i.e., protective) side. The study used to derive the AEGL-2 values was additionally supported by two other multiple-exposure studies, one using CMME with rats and hamsters (Laskin et al., 1975) and the other testing BCME with rats and mice (Leong et al 1975, 1981).

An adequate single-exposure study rat was available for derivation of AEGL-3 values (Drew et al., 1975), and was supported by a similar response in a second species (i.e., hamsters).

The BCME content of the CMME used in the key AEGL-2 and AEGL-3 study should have been specified. Data quantifying the amount of BCME in typical batches of CMME are needed, and could be used to refine the modifying factor needed to account for the variability in BCME content of CMME for the AEGL derivations.

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APPENDIX A:
Derivation of AEGL Values

AEGL-1

AEGL-1 values were not derived because there were no studies using technical grade CMME that produced endpoints consistent with the definition of AEGL-1.

AEGL-2

Key study: Drew et al., 1975. Rat technical grade CMME 30-exposure study. AEGL-2 values were derived based on one 6-hour exposure, which would cause a similar or lower incidence of lung hyperplasia and/or metaplasia than 30 exposures.

Toxicity endpoint: Pulmonary hyperplasia; broncheotracheal squamous metaplasia

Scaling: $C^n \times t = k$ (ten Berge et al., 1986); no data were available to derive n. To obtain protective AEGL values, used n=3 to extrapolate to < 6 hours and n=1 to extrapolate to > 6 hours except the 10-minute value is same as 30-minute value because extrapolating from 6 hours to 10 minutes is associated with unacceptably large inherent uncertainty.

For ½, 1, and 4 hours: $(1 \text{ ppm})^3 (6 \text{ hrs}) = k = 6$ ppm-hrs
For 8 hours: $(1)^1 (6 \text{ hrs}) = k = 6$ ppm-hrs
For 10 minutes: adopt 30-minute value

Total uncertainty factor: 10
Intraspecies: 3 - Response to an irritant gas hydrolyzed *in situ* is not likely to vary greatly among humans.
Interspecies: 3 - Key study was multiple exposure and little interspecies variability was seen, as expected for an irritant gas hydrolyzed *in situ*.

Modifying factor: 3: for potential variability in BCME content of technical grade CMME

Calculations: $C^3 \times 0.5 \text{ hour} = 6 \text{ ppm.hr}$
$C = 2.29$ ppm
30 minute (and 10-minute) AEGL-2 = 2.29/30 = **0.076 ppm** [0.25 mg/m^3]

$C^3 \times 1 = 6$ ppm.hr
$C = 1.82$ ppm
1 hour AEGL-2 = 1.82/30 = **0. 061 ppm** [0.20 mg/m^3]

$C^3 \times 4 \text{ hours} = 6$ ppm.hr
$C = 1.14$ ppm
4 hour AEGL-2 = 1.14/30 = **0.038 ppm** [0.13 mg/m^3]

$C^1 \times 8 \text{ hours} = 6$ ppm.hr
$C = 0.75$ ppm
8 hour AEGL-2 = 0.75/30 = **0.025 ppm** [0.082 mg/m^3]

AEGL-3

Key study: Drew et al., 1975. Rat 7-hour exposure inhalation LC_{50} study.

Toxicity endpoint: Lethality threshold, estimated from LC_{01} values obtained by probit analysis: 7- hour LC_{01} = 14.8 ppm

Scaling: $C^n \times t = k$ (ten Berge et al., 1986); no data were available to derive n. To obtain protective AEGL values, used n=3 to extrapolate to < 7 hours and n=1 to extrapolate to > 7 hours except the 10-minute value is same as 30-minute value because extrapolating from 6 hours to 10 minutes is associated with unacceptably large inherent uncertainty.

For ½, 1, and 4 hours: $(14.8 \text{ ppm})^3 (7 \text{ hrs}) = k = 22693$ ppm-hrs
For 8 hours: $(14.8)^1 (7 \text{ hrs}) = k = 103.6$ ppm-hrs
For 10 minutes: adopt 30-minute value

Total uncertainty factor: 10
Intraspecies: 3 - Response to an irritant gas hydrolyzed *in situ* is not likely to vary greatly among humans.
Interspecies: 3 - Little interspecies variability was seen (rat and hamster had similar 7-hour LC_{50} values), as expected for an irritant gas hydrolyzed *in situ*.

Modifying factor: 3: for potential variability in BCME content of technical grade CMME

Calculations: $C^3 \times 0.5$ hour = 22693 ppm.hr
C = 35.67 ppm
30 minute (and 10-minute) AEGL-3 = 35.67 ppm/30 = **1.2 ppm** [3.9 mg/m^3]

$C^3 \times 1$ hour = 22693 ppm.hr
C = 28.31 ppm
1 hour AEGL-3 = 28.31 ppm/30 = **0.94 ppm** [3.1 mg/m^3]

$C^3 \times 4$ hours = 22693 ppm.hr
C = 17.84 ppm
4 hour AEGL-3 = 17.84 ppm/30 = **0.59 ppm** [2.0 mg/m^3]

$C^1 \times 8$ hours = 103.6 ppm.hr
C = 12.95 ppm
8 hour AEGL-3 = 12.95 ppm/30 = **0.43 ppm** [1.4 mg/m^3]

APPENDIX B:
Carcinogenicity Assessment

PRELIMINARY CANCER ASSESSMENT OF CMME, BASED ON EPA CANCER ASSESSMENT OF BCME

A cancer assessment of bis-chloromethyl methyl ether (BCME) was performed by the U.S. EPA (IRIS, 1998) using data from Kuschner et al. (1975). Male Sprague-Dawley rats given 0, 10, 20, 40, 60, 80, or 100 six-hour, 0.1 ppm exposures (lifetime observation) had increased incidence of nasal and/or lung tumors (total incidence of 0/240, 1/41, 3/46, 4/18, 4/18, 15/34, 12/20, respectively). The calculated inhalation unit risk **for BCME** was 6.2×10^{-2} per ($\mu g/m^3$), using the linerarized multistage procedure, extra risk extrapolation method (IRIS, 1998). The corresponding air concentration at a risk level of 10^{-4} was 1.6×10^{-3} $\mu g/m^3$.

For 10^{-4} risk from lifetime (24-hour/day) exposure, total BCME exposure would be:

$(16 \times 10\text{-}3^{-3}\ \mu g/m^3)$ (25.600 days= 40.96 $\mu g/m^3$ **BCME**
(Risk) (70-Years life)

An additional adjustment factor of 6 is applied to account for uncertainty regarding the stages of the carcinogenic process at which BCME acts (Crump and Howe, 1984):

40.96 $\mu g/m^3 \div 6 = 6.83$ $\mu g/m^3$ **BCME**

Converted to "pure" CMME, this concentration would be,

6.83 $\mu g/m^3$ **BCME** ÷ 0.08 85.4 $\mu g/m^3$ **CMME** = <u>0.026 ppm CMME *for 24-hour exposure*</u>

NOTE: ASSUMES <u>CMME</u> CARCINOGENICITY IS DUE SOLELY TO <u>BCME</u>

For exposures less than 24 hours, the fractional exposure (f) becomes 1/f x 24 hours (NRC, 1985): (Extrapolation to 10 minutes was not calculated due to unacceptably large inherent uncertainty; see Section 4.4.2.):

Exposure duration	AEGL values (ppm) for 10^{-4} cancer risk	AEGL values (ppm) for 10^{-5} cancer risk	AEGL values (ppm) for 10^{-6} cancer risk
½ hour	1.2	0.12	0.012
1 hour	0.62	0.062	0.0062
4 hours	0.16	0.016	0.0016
8 hours	0.078	0.0078	0.00078
24 hours	0.026	0.0026	0.00026

(If the CMME content is only 1% and not 8%, all the AEGL values would be multiplied by 8.)

Because the derivation of the cancer slope factor requires conversion of animal doses to human equivalent doses, no reduction of exposure levels is applied to account for interspecies variability.

CMME AEGL-2 values based on the noncarcinogenicity endpoints were lower than those calculated for 10^{-4} excess cancer risk but were similar to or greater than those calculated for 10^{-5} or 10^{-6} excess cancer risk. AEGL-2 values based on the noncarcinogenic endpoints were considered to be more appropriate because only multiple exposures to CMME were shown to result in tumor formation and AEGL values are applicable to rare events or single, once-in-a-lifetime exposures of small populations in limited geographic areas.

APPENDIX C:
Derivation Summary for Chloromethyl Methyl Ether AEGLs

ACUTE EXPOSURE GUIDELINES FOR CHLOROMETHYL METHYL ETHER (107-30-2) DERIVATION SUMMARY

AEGL-1 VALUES FOR TECHNICAL GRADE CHLOROMETHYL METHYL ETHER (107-30-2)				
30-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
Not Recommended (No studies available within scope of AEGL-1 definition)				
Key Reference: Not applicable				
Test Species/Strain/Number: Not applicable				
Exposure Route/Concentrations/Durations: Not applicable				
Effects: Not applicable				
Endpoint/Concentration/Rationale: Not applicable				
Uncertainty Factors/Rationale: Total uncertainty factor: Not applicable Interspecies: Intraspecies:				
Modifying Factor: Not applicable				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: Not applicable				
Data Quality and Support for AEGL-1 Values: AEGL-1 values for technical grade CMME were not derived because there were no studies that had endpoints consistent with the definition of AEGL-1.				

AEGL-2 VALUES FOR TECHNICAL GRADE CHLOROMETHYL METHYL ETHER (107-30-2) [ppm (mg/m^3)]

10-minute	30-minute	1-hour	4-hour	8-hour
0.076 (0.25)	0.076 (0.25)	0.061 (0.20)	0.038 (0.13)	0.025 (0.082)

Key Reference: Drew, R.T., S. Laskin, M. Kuschner, N. Nelson. 1975. Inhalation carcinogenicity of alpha halo ethers. I. The acute inhalation toxicity of chloromethyl methyl ether and bis(chloromethyl)ether. Arch. Environ. Health 30:61-69

Test Species/Strain/Sex/Number: Male Sprague-Dawley rats; 25/ test concentration

Exposure Route/Concentrations/Durations: Inhalation; 1 ppm or 10 ppm: 30 exposures for 6 hours; sacrifice after 30 exposures, 2 weeks after the 30 exposures, or after lifetime observation

Effects: 1 ppm (held for life): regenerative hyperplasia (2/13) or tracheobronchial squamous metaplasia (2/13); one death on 16th and one on 22nd exposure day; cause of death not given
10 ppm: increased lung-to-body weight ratios, bronchial epithelial hyperplasia; 22/25 died by day 30

Endpoint/Concentration/Rationale: Pulmonary hyperplasia and/or broncheotracheal squamous metaplasia. AEGL-2 values were based on a single 6-hour exposure to 1 ppm, reasoning that one 6-hour exposure would cause a similar or lower incidence of hyperplasia and/or metaplasia than 30 exposures, and which mitigates the uncertainty associated with the two animal deaths after days 16 and 22 (cause of death not given).

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Intraspecies: 3 - Response to an irritant gas hydrolyzed *in situ* is not likely to vary greatly among humans.
Interspecies: 3 - The key study was multiple exposure; little interspecies variability was seen, as expected for an irritant gas hydrolyzed *in situ*.

Modifying Factor: 3 - To account for potential variability in the BCME content of technical grade CMME

Animal to Human Dosimetric Adjustment: Not applied

Time Scaling: $C^n \times t = k$ (ten Berge et al., 1986); no data were available to derive n. To obtain protective AEGL values, used n=3 and n=1 to extrapolate to < 6 hours and > 6 hours, respectively, except the 10-minute value is same as 30-minute value because extrapolating from 7 hours to 10 minutes is associated with unacceptably large inherent uncertainty.

Data Quality and Support for AEGL-2 Values: Although the key study was 30-exposure, it has the benefit of lifetime animal observation, which is pertinent for a suspected cancer-causing agent. The derived values are supported by a lifetime CMME exposure rat and hamster study and a 6-month BCME rat and mouse study.

AEGL-3 VALUES FOR TECHNICAL GRADE CHLOROMETHYL METHYL ETHER (107-30-2) [ppm (mg/m^3)]

10-minute	30-minute	1-hour	4-hour	8-hour
1.2 (3.9)	1.2 (3.9)	0.94 (3.1)	0.59 (2.0)	0.43 (1.4)

Key Reference: Drew, R.T., S. Laskin, M. Kuschner, N. Nelson. 1975. Inhalation carcinogenicity of alpha halo ethers. I. The acute inhalation toxicity of chloromethyl methyl ether and bis(chloromethyl)ether. Arch. Environ. Health 30:61-69

Test Species/Strain/Sex/Number: Male Sprague-Dawley rats; number not given but was >10/concentration

Exposure Route/Concentrations/Durations: Inhalation: 12.5, 26, 42, 54, 70, 141, or 225 ppm for 7 hours; observed for 14 days

Effects:

Conc.	% Mortality	% Inc. lung/bw ratio	
225 ppm	100	80	
141 ppm	100	80	LC_{50}: 55 ppm (provided in reference)
70 ppm	100	90	LC_{01}: 14.8 ppm (probit analysis)
54 ppm	43	67	
42 ppm	225 (25)*	55	
26 ppm	110 (10)*	20	
12.5 ppm	0	0	

*The % mortality given appeared to be a typographical error; suggested values are in parentheses.

Endpoint/Concentration/Rationale: Threshold for lethality, based on LC_{01} value (14.8 ppm) obtained by probit analysis.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Intraspecies: 3 - Response to an irritant gas hydrolyzed *in situ* is not likely to vary greatly among humans.
Interspecies: 3 - Little Interspecies variability was seen (rat and hamster had similar 7-hour LC_{50} values), as expected for an irritant gas hydrolyzed *in situ*.

Modifying Factor: 3 - To account for variability in the BCME content of technical grade CMME

Animal to Human Dosimetric Adjustment: Not applied

Time Scaling: $C^n \times t = k$ (ten Berge et al., 1986); no data were available to derive n. To obtain protective AEGL values, used n=3 and n=1 to extrapolate to < 7 hours and > 7 hours, respectively, except the 10-minute value is same as 30-minute value because extrapolating from 7 hours to 10 minutes is associated with unacceptably large inherent uncertainty.

Data Quality and Support for AEGL-3 Values: The key study was well-conducted and the derived AEGL-3 values are supported by a CMME hamster LC_{50} study and by a BCME single-exposure rat study.